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DRAFT MEMORANDUM

FROM: Douglas C. Throckmorton, M.D., Medical Officer
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/s/ [redacted]

THROUGH: Shaw Chen, M.D., Medical Team Leader
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TO: Victoria Lutwak, Project Manager
James Witter, Medical Officer
John Hyde, M.D., Ph.D., Deputy Division Director
Robert DeLap, M.D., Ph.D., Acting Division Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (DAAODP), HFD-550

SUBJECT: NDA 20-998
NAME OF DRUG: Celecoxib (SC-58635)
TRADE NAME Celebrex
FORMULATION: Capsules for oral administration.

RELATED APPLICATIONS: None

PROPOSED INDICATIONS: 1) Acute and chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis; and
2) Management of pain.

SPONSOR: Searle

DATE CONSULT RECEIVED: 7.15.98
DATE DRAFT CONSULT COMPLETED: 11.6.98

ISSUES TO BE ADDRESSED: 1) Review of NDA 20-998 Cardiac and Renal Safety Database.
2) Review of three 'Renal' studies in NDA 20-998.

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/s/ [redacted]
Douglas C. Throckmorton, M.D.

0.0 Overall Renal and Cardiac Safety Consultant Summary

General Summary

During the development of specific inhibitors of the type 2 isoform of cyclooxygenase (COX-2), it was hoped that they would provide selective anti-inflammatory efficacy without concomitant GI and renal toxicity. This was based on animal work that suggested that the GI system and kidneys did not express the COX-2 isoform. More recent work has demonstrated the clear presence of COX-2 in the kidney, both in normal adult kidney and in patients with systemic lupus erythematosus. Work in animals has also suggested the up-regulation of COX-2 following volume contraction. These data suggest, at the very least, that the target of COX-2 inhibitors is present in the kidney, and they provide a plausible mechanism for any observed clinical renal toxicity. That this target (COX-2) may be increased during times of sodium- and water-depletion suggests a role for COX-2 in protecting renal hemodynamics. Whether this observation translates into an increased risk of nephrotoxicity in clinical states associated with potentially impaired renal perfusion, such as volume contraction, is not known at present.

Cardiac and renal safety was examined in both the short-term, controlled trials, and in the longer, open-label trial of patients with osteoarthritis/rheumatoid arthritis (OA/RA). Overall, 6376 patients were exposed to celecoxib during the short-term, controlled, North American trials in OA/RA. During the open-label trials, another 9822 patients received celecoxib. Of these, the large majority received the drug for <180 days. With regard to long-term exposure, 1809 OA/ RA patients received celecoxib for periods lasting for between 12 weeks and > 1 year in an open-label trial.

As part of the safety database, the sponsor collected adverse events related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients. Significantly, no measurements of acid-base balance database (e.g., serum bicarbonate, arterial pH) were performed as part of any trial in the NDA. With this exception, the database was sufficient to assess the clinically relevant renal and cardiac toxicities.

Cardiac Safety

The administration of celecoxib cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some adverse events, including arrhythmias and overall cardiovascular mortality, the data are inadequate to either exclude or confirm an adverse effect of celecoxib.

With regard to **cardiovascular adverse events**, there is an association between celecoxib administration and **worsened hypertension** in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There was also an association between celecoxib administration and the development of clinically significant **edema**, again similar to other NSAIDs.

Renal Safety

Three trials were performed on specific populations (elderly patients, patients with mild-to-moderate renal insufficiency, patients with volume contraction) to examine their renal responses to celecoxib. These trials examined the short-term effects of celecoxib on the excretion of prostaglandins, as well as a variety of other renal parameters. The trials enrolled small numbers of patients for short trial durations. Under the conditions of those trials, both celecoxib and the comparator NSAIDs inhibited prostaglandin PGE_2 and 6-keto-PGF_1-alpha by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of these urinary prostaglandins when compared with placebo.

There was sufficient evidence to conclude that celecoxib has significant **renal effects**, as reflected in the pattern of lab abnormalities associated with celecoxib administration. This pattern includes an association between celecoxib and several lab abnormalities: **hyperchloremia, hypophosphatemia, and elevated BUN in association with proteinuria**. These surrogates for renal toxicity suggest, but do not confirm, a link between celecoxib use and clinically relevant nephrotoxicity. Further, the incidence of the lab abnormalities occurred to a similar extent in both the celecoxib and the active control groups, suggesting that both celecoxib and the other NSAIDs have similar renal effects.

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Within the limitations of the database there is no evidence to suggest that celecoxib has unique renal toxicities not shared with other NSAIDs, or a toxicity also caused by NSAIDs that occurs at a significantly higher incidence rate. In the absence of bicarbonate data, an adverse effect of celecoxib on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia. While there were no clear cases of celecoxib-induced renal failure in the controlled database, there were several individuals taking celecoxib who were withdrawn from the long-term open-label trial because of renal adverse events, including acute renal failure (as well as, edema and worsening hypertension). It remains to be determined is whether renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

While a through comparison of the renal effects of celecoxib and other NSAIDs has not been performed, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib are clearly distinguished from placebo.

1.0 Materials Utilized in Review

1.1 Materials from NDA

1. NDA 20-998, volumes: 1.1-1.3; 1.129; 1.134-1.43; 1.425-1.442.
2. NDA 20-998, submitted in CANDA format.

1.2 Other Resources

No separate consultations, including outside experts or advisory committee proceedings, were obtained during this NDA review. Where appropriate, the results of the literature review are included in the Mechanisms of Action section below, and in the integrated Safety Summary (section 4.1-4.2).

2.0 to 2.7 Background Information

The background information below is drawn from the sponsor's summary and from the published literature. Please see pertinent primary reviews for further details.

2.1 Chemistry

Celecoxib is a diarylsubstituted pyrazole and has the following structural formula: 4-[5-(4- methylphenyl)-3-(trifluoromethyl)- 1H- pyrazol- 1- yl] benzenesulfonamide.

2.2 Mechanism of Action

Celecoxib is a member of a novel class of anti- inflammatory and analgesic agents known as specific cyclooxygenase type 2 (COX-2) inhibitors. Celecoxib causes persistent inhibition of COX-2 through an interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX-2. In animal models, inhibition of COX-2 has been observed to have anti-inflammatory, analgesic, antipyretic and anti- proliferative effects. In animals, these effects of celecoxib occur at concentrations that inhibit COX- 2 *in vitro*. At therapeutic concentrations, the sponsor reports that celecoxib does not inhibit the constitutive isoenzyme (COX- 1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

There is limited information about the role that COX-2 plays in the kidney. In rats and dogs, COX-2 is constituitively expressed in the macula densa and adjacent epithelial cells of the cortical collecting duct (references 1,2). The authors of these papers speculate that COX-2 was critical for the response to volume-contraction, perhaps by regulating renin release from the macula densa. It has also been reported that COX-2 is not normally present in adult human kidneys, but is up-regulated in lupus nephritis reference 3).

2.3 Pharmacokinetics/ pharmacology/ pharmacodynamics

Pharmacokinetics: The pharmacokinetics of celecoxib have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment. The table below summarizes the pharmacokinetics of celecoxib (per the sponsor).

Table 2.3.1 Summary of single dose disposition kinetics of celecoxib in healthy subjects[a].

Parameter	Mean (90 % CI)
C_{max}, (ng/ mL)	598 (54)
T_{max}, (hr)	3.42 (45)
AUC (48), (ng/ mL)* hr	6270 (30)
AUC (inf), (ng/ mL)* hr	6694 (30)
$T_{1/2}$, (hr)	11.7 (39)
V_z /F, (L/ 70 kg)	533 (51)
CL/ F, (L/ hr/ 70 kg)	31.7 (34)
Relative bioavailability, (%)	99 (95- 104)

a. Data from proposed labeling, NDA 20-998 vol. 1.1

Pre-clinical renal pharmacology and pharmacodynamics

Celecoxib was tested for its effect on urinary volume and electrolyte excretion in rats at oral doses from 5 to 500 mg/kg. Celecoxib decreased urinary volume (b)(4) with a plateau in effect from (b)(4) Sodium excretion was decreased with celecoxib doses from 50 to 500 mg/kg by (b)(4) with a plateau in effect from (b)(4) Chloride excretion was decreased by celecoxib doses from 50 to 500 mg/kg by 16 to 35% with a plateau in effect from 150 to 500 mg/kg. Urinary osmolarity was increased by celecoxib doses of 15 to 500 mg/kg by (b)(4) with a plateau in effect from 150 to 500 mg/kg.

In a high-dose study, celecoxib was administered 600 mg/kg/day to male rats for 7 days. In this study, celecoxib had no effect on urinary volume or urinary excretion of PGE_2. Plasma levels of celecoxib reached 6.99 g/mL on day 7 at 5 h after dosing. As a control, indomethacin (4 mg/kg/day) lowered PGE2 urinary levels and volume only on day 3.

2.4 Metabolism

Metabolism: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. The methyl group of celecoxib is hydroxylated to a primary alcohol that is further metabolized to a carboxylic acid. A minor amount of the carboxylic acid metabolite is conjugated to glucuronic acid to form the 1- O- glucuronide. The metabolites are inactive as COX- 1 or COX- 2 inhibitors. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochromes P450 2C9, 2C19 or 3A4, and though not a substrate, is a relatively weak inhibitor of cytochrome P450 2D6. However, celecoxib at plasma concentrations achieved in humans, at the recommended doses, is not expected to substantially inhibit the metabolism of other drugs that are metabolized via the 2D6 isozyme. Clinical data to confirm this expectation are not available.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine. Celecoxib is excreted as the acid metabolite predominantly in the feces (approximately 54% of the administered dose) and to a lesser extent in the urine (approximately 18% of the administered dose).

2.5.1 Renal Toxicology

1) 2-week administration to mice

Lesions consistent with test-article associated renal injury were found to three males (95S0745, 95S0746, and 95S0747) and four females (95S0754, 95S0755, 95S0756, and 95S0762) from the 1000 mg/kg/day dosage group. All seven animals demonstrated a nephropathy characterized by focal degeneration of renal tubules with regeneration, epithelial basophilia, intraluminal casts (cellular or hyaline) and a minimal mononuclear cell interstitial infiltrate. In all animals the lesion was slight to mild except for one 1000 female (95S0754) where it involved the cranial 1/3 of the left kidney (corresponding to a macroscopic lesion). The sponsor noted that while these lesions are sometimes seen in aged mice, but would not be expected in mice this age.

One incidence of renal papillary necrosis (moderate, Grade 3 of 5) was also seen in a male receiving 1000 mg/kg/day.

2) 4-week administration to dogs

No histologic damage was reported in the 25 mg/kg dose group. Slight to moderate acute renal papillary necrosis was diagnosed in four animals including one male given 50 mg/kg, two females given 100 mg/kg, and one male given 250 mg/kg. Notable was the slight acute unilateral papillary necrosis that was seen in one female in the 100 mg/kg reversal group.

Per the sponsor, later studies using lower-doses of celecoxib did not demonstrate any histologic evidence of renal toxicity. The sponsor then concluded that the 'absence of renal papillary necrosis in chronic rodent studies' suggested that celecoxib 'is different from NSAIDs.'

2.5.2 Cardiac Toxicology

1) Acute infusion to guinea pigs

The cardiopulmonary effects of celecoxib were examined in an acute guinea pig model. The only effect notes, per the sponsor, was a small but significant increase in systolic blood pressure.

2) Acute administration to anesthetized dogs

The only significant effect noted in this model was an increase in left-ventricular end-diastolic pressures seen at the higher doses in 2/4 dogs. No effect on blood pressure or other vital signs was detected.

2.6 Proposed Renal and Cardiac Labeling

Below are sections of the proposed label that pertain to celecoxib renal efficacy and/or safety. The statements for each section are per the sponsor, and come from the proposed labeling section of the NDA. A discussion of the appropriateness of each of the statements will be included in the Integrated Safety Summary (section 5.3 and 5.4).

Dosing: The maximum proposed dose of celecoxib 400 mg per day in divided doses.

Pharmacodynamics: Celecoxib causes persistent inhibition of COX- 2 through a novel interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX- 2. At therapeutic concentrations celecoxib does not inhibit the constitutive isoenzyme (COX-1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

Pharmacokinetics: The pharmacokinetics of Celebra have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine.

Special studies (Safety)

Renal: Celebra has no deleterious effects on renal function. Administration of Celebra at doses of 200 and 400 mg BID for periods of 7- 10 days was studied in elderly subjects and patients with moderate renal impairment.

Dosage Adjustment in Special Populations

Renal insufficiency: Because celecoxib is predominantly metabolized by the liver and none of the metabolites are pharmacologically active, no dosage adjustment is necessary in patients with mild to moderate renal insufficiency. In elderly volunteers with age related reductions in GFR (> 65 mL/ min/ 1.73 m^2) and in patients with moderate renal insufficiency (b)(4) celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine and estimated creatinine clearance and celecoxib clearance. Patients with severe renal insufficiency have not been studied and therefore should use the lowest effective dose.

Precautions

General

Because Celebra has no effect on platelet function, it should not be used for cardiovascular prophylaxis.

***Renal effects*:** The effect of Celebra in advanced renal disease (GFR <40 mL/ min/ 1.73m^2) has not been studied. No prospective studies have been conducted in patients with considerable dehydration, advanced renal disease, congestive heart failure or liver dysfunction.

Use in Elderly: In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

ACE-Inhibitors and Diuretics

Although prospective studies of Celebra with ACE inhibitors and diuretics have not been conducted, no increased incidence of adverse reactions indicative of elevations in blood pressure were seen in clinical trials in which arthritis patients were taking Celebra concurrently with ACE inhibitors, or diuretics. No increased incidence of adverse reactions indicative of sodium retention or renal impairment were seen in clinical trials in patients taking Celebra concurrently with diuretics.

Aspirin:

Celebra has been administered to patients taking aspirin up to 325 mg per day. Low doses of aspirin have been associated with ulcers. Thus concomitant use of Celebra with aspirin may result in an increased rate of GI ulceration compared to when Celebra is used alone.

3.0 Description of Clinical Data Sources

3.1 Primary Source Data

A total of 29 clinical pharmacology and 22 phase II/III clinical efficacy trials were performed as part of the celecoxib development. Of these, 13 clinical trials were performed to compare celecoxib with other NSAIDs. Three of these latter studies focused on the renal effects of celecoxib: study 010 (Renal effects in the elderly); study 033 (Na+/volume depletion and renal effects); and study 036 (Renal effects in chronic renal insufficiency). These three trials will be examined individually.

In total, the safety database used for this consult includes 13,072 individuals enrolled in clinical trials. More than 75% of these individuals had either osteo- or rheumatoid- arthritis, and enrolled in trials of ≥2 weeks duration.

3.1.1 Study Type and Design/Patient Enumeration

3.1.2 Demographics

The first table summarizes the subject exposure to celecoxib in the entire database.

Table 3.1.2.1 Summary of Celecoxib-treated subjects in the NDA 20-998 database[a].

Study Design	# Of Treated Subjects	# of Unique Subjects[b]
Phase I: Single Dose	294	251
Phase I: Multiple Dose	398	270
Phase I: Drug Interactions	260	131
Phase I: Hepatic	48	48
Phase I: Renal	23	23
Arthritis: OA	4280	4151
Arthritis: RA	2096	2086
Arthritis: Long-term Open-label	4499	1757
Analgesia: Dental pain	531	529
Analgesia: Surgical pain	217	217
Combined Studies	12646	9463

a. Data from NDA Integrated Summary of Safety Information, table 2.11.
b. Does not count individuals more than once who received celecoxib as part of more than one trial.

3.1.3 Extent of Exposure (dose/duration)

Dose Exposure to Celecoxib

The next table summarizes the celecoxib exposure according to the dose of celecoxib for all studies in the NDA.

Table 3.1.3.1 Summary of celecoxib exposure by dose from NDA 20-998[a].

Treatment and Dose	Treated Subjects	Unique Treated Subjects
Celecoxib Single Dose (5-1200 mg)	825	780
Celecoxib Multi-Dose		
5-50 mg	959	948
100 mg	4872	3261
200 mg per day	564	500
200 mg	4562	3272
400 mg	721	665
600 – 1200 mg	20	20
Celecoxib +Other Drug	123	17
Total	12646	9463
Comparator Agents		
Placebo	2450	1354
Active Controls	3343	2255
Total	5793	3609
Overall Total	18439	13072

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 5.

3.1.3 Extent of Exposure (dose/duration) (cont)

Duration Exposure to Celecoxib

The chronic exposure data comes from the trials in osteoarthritis (OA) or rheumatoid arthritis (RA). This will be the database used primarily for the assessment of renal and cardiac safety. The table below summarizes the duration of patient exposure in the OA/ RA database, broken into three categories: 0-6 weeks; 6 weeks to 6 months; and greater than 6 months. Note that there are very few subjects who received celecoxib with long-term (>180 days) exposure to celecoxib in a controlled trial (n=39). A larger number received celecoxib in open-label trials for >180 days (n=1809).

Table 3.1.3.2 Duration of arthritis patient exposed to celecoxib in the NDA 20-998 database[a].

	25-50 mg	100 mg	200 mg	300 mg	400 mg	Total[b]
OR-RA Controlled Trials						
1-42 days	462	888	818	0	308	2476
43-180 days	481	1237	1836	0	307	3861
>180 days	0	0	39	0	0	39
OA-RA Uncontrolled (Open-Label) Trials						
1-42 days	110	1689	1527	768	200	4294
43-180 days	310	970	1509	451	489	3729
>180 days	0	236	941	222	410	1809
Total	1363	5020	6670	1441	1714	16208

a. Data from NDA 20-998, vol. 1.426, Table 3.4

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The sponsor also summarized exposure to celecoxib in patient-years of exposure for all subjects in the arthritis trials. The results are shown below.

Table 3.1.3.3 Duration of exposure to celecoxib, by patient-years, in the NDA 20-998 database[a].

	50 mg	100 mg	200 mg qD	200 mg BID	300 mg	400 mg	Any Dose[b]
OR-RA Controlled Trials	116	289	47	466	0	87	1020
OA-RA Uncontrolled (Open-Label) Trials	75	518	0	1271	340	465	2672
OA-RA Controlled & Uncontrolled Trials	117	680	47	1567	340	499	3267

a. Data from NDA 20-998, Integrated Summary of Safety, Table 4.3. Patients are counted only once per treatment group.

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The demographics of the subjects enrolled in the North American arthritis trials are summarized below.

Table 3.1.3.4 Demographics of the North American arthritis trials in NDA 20-998[a].

Demographic	Placebo N=1864	Celecoxib N=5704	Active Controls N=2098
Age			
Mean	60.0	59.5	58.8
>64	731 (39.2%)	2117 (37.1%)	737 (35.1%)
Ethnicity			
White	1629 (87.4%)	4844 (84.9%)	1792 (85.4%)
Black	156 (8.4%)	580 (10.2%)	216 (10.3%)
Hispanic	67 (3.6%)	219 (3.8%)	78 (3.7%)
Asian	4 (0.2%)	34 (0.6%)	6 (0.3%)
Other	8 (0.4%)	27 (0.5%)	6 (0.3%)
Gender			
Female	1324 (71.0%)	3986 (69.9%)	1427 (68.0%)
Male	540 (29.0%)	1718 (30.1%)	671 (32.0%)

a. Data from NDA Integrated Safety Summary, table 6.1.

3.1.3 Extent of Exposure (dose/duration) (cont)

The sponsor collected information on the past medical histories of the subjects enrolled in the trials as well. Below are the incidences of relevant cardiac and renal medical history (arranged according to ICD-9 codes) in the North American controlled trials. Unlisted ICD-9 codes occurred at <1.0% or were considered non-significant for purposes of this review. Overall, a significant fraction of the subjects had hypertension. A much smaller % had a history of significant cardiac disease or renal disease. No information about smoking history is available.

Table 3.1.3.5 Significant cardiac and renal past medical history in the celecoxib North American controlled trials[a].

	Placebo N=1864[b]	Celecoxib 25-400 mg N=5704[c]	Active Controls N=2098[d]
Cardiovascular Disease			
Angina Pectoris	57 (3.1%)	194 (3.4%)	75 (3.6%)
Coronary Atherosclerosis	70 (3.8%)	201 (3.5%)	82 (3.9%)
Congestive Heart Failure	24 (1.3%)	63 (1.1%)	25 (1.2%)
Hypertension (not otherwise specified)	732 (39.3%)	2172 (38.1%)	749 (35.7%)
CABG	31 (1.7%)	118 (2.1%)	39 (1.8%)
Myocardial Infarction (not otherwise specified)	54 (2.9%)	167 (2.9%)	74 (3.5%)
Endocrine Disease			
Diabetes Type I (uncomplicated)	26 (1.4%)	89 (1.5%)	34 (1.6%)
Diabetes Type II (uncomplicated)	114 (6.1%)	408 (7.2%)	156 (7.4%)
Hypothyroid	234 (12.6%)	659 (11.6%)	241 (11.5%)
Hyperlipidemia	108 (5.8%)	376 (6.6%)	137 (6.5%)
Obesity	131 (7.0%)	389 (6.8%)	148 (7.1%)
Renal/ GU Disease			
Renal calculus	64 (3.4%)	206 (3.6%)	93 (4.4%)
Hematuria	29 (1.6%)	65 (1.1%)	17 (0.8%)
UTI	95 (5.1%)	231 (4.0%)	76 (3.6%)

a. Data from NDA Integrated Safety Summary, Appendix 8.2. The database used is includes studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Collected ICD-9 codes were used to calculate incidence rates for each group.

Regarding the demographics of the subjects in the long-term, open-label study, these will be similar to those in the table above. This is because all of the subjects in the open-label trial first enrolled (and completed) one of the shorter trials prior to entry into the open-label, long-term trial.

The renal effects of celecoxib specifically in three small trials and as part of the overall safety database. The three 'Renal Effects' trials are reviewed in section 4.0. Note that the longest period of exposure to study drug was 7 days in these three trials.

Table 3.1.3.6 Summary of 'Renal Effects' Trials in the NDA 20-998 database.

Study #	Short Title	Duration of Exposure to Study Drug	# of Control Subjects[a]	# of Celecoxib Subjects
010	Renal Effects in the Elderly	10 Days	27	26
033	Na^+/Volume Depletion and Renal Effect	7 Days	21[a]	21
036	Renal Effects in Chronic Renal Insufficiency	7 Days	52[a]	23

a. Includes subjects who received active controls.

3.1.4 Renal Data Collected in the NDA Database

Renal adverse events were collected both during the 3 trials summarized above, and as part of the overall adverse event reporting for the rest of the clinical program. In the three 'Renal Effects' trials specific measures of renal function were measured (i.e., urine prostaglandin excretion). These will be discussed in the trial summaries below. For the clinical trials as a whole, adverse events were identified either through periodic meetings between the subjects and investigators, or through the use of subject diaries. Serious adverse events were likewise identified, and transmitted to the sponsor immediately.

For evaluation of clinical laboratory results, the sponsor set upper and lower limits representing values of potential clinical relevance, along with cutoff values considered to represent lower and upper extremes. The table below shows the relevant boundaries for the renal laboratory adverse events. Note that no extreme value for bicarbonate was established. At this reviewer's request, the sponsor stated that... 'we have checked the clinical studies in our NDA 20-998 and can confirm that there are no studies which tested for bicarbonate either by gas determination or in serum.' (Letter, 8.7.98).

Table 3.1.4.1 Mid-range and extreme value limits for evaluation of clinical lab results in NDA 20-998[a].

Lab Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Upper Extreme
Serum Measurements				
Creatinine	N/A	N/A	176.8 µmol/L (=2 mg/dl)	265.2 µmol/L (=3 mg/dl)
BUN	N/A	N/A	9.3 mmol/L (=27 mg/dl)	14.3 mmol/L (=42 mg/dl)
Sodium	120 mmol/L	135 mmol/L	140 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	6.0 mmol/L
Chloride	75 mmol/L	90 mmol/L	110 mmol/L	130 mmol/L
Calcium	>15% below Baseline, or <1.7 mmol/L	2.0 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Blood	N/A	N/A	Trace	1+
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
pH	N/A	4	8	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	N/A	5/hpf	10/hpf
WBC	N/A	N/A	10/hpf	20/hpf
Ketones	N/A	N/A	Trace	1+
Urine bilirubin	N/A	N/A	Trace	1+

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 3.

3.1.5 Cardiac Data Collected in the NDA Database

While no trials specifically addressed the question of cardiovascular effects of celecoxib, certain elements of cardiovascular safety were collected as part of the assessment of each subject: blood pressure; heart rate; weight. The occurrence of lab abnormalities for creatine phosphokinase was also collected. As part of the safety database, other cardiovascular adverse events (AEs) were collected, including the occurrence of: cardiac ischemia, arrhythmias, strokes, and hypertension.

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3.2 Data from Secondary Sources/ Published Literature

Aside from the published literature, no secondary sources of data were used in this consult. Two approaches were used to identify relevant published literature relevant to the current submission.

First, this reviewer conducted an independent literature review, through a keyword search of Medline. Second, the sponsor has provided a literature review, which was cross-referenced with the above reviews to assure completeness. The cut-off for consideration of articles in this NDA was approximately January of 1998. This literature review has been incorporated into the background section of this introduction, and into the integrated safety summary where appropriate. References appear at the end of the Integrated Renal/ Cardiac Safety Summary, section 5.3.

3.3.1 Comment on Adequacy of Clinical Experience

The database includes a total of 9463 subjects in the clinical database who were exposed to celecoxib. With regard to the number of subjects exposed, a total of 7718/ 9463 subjects (82%) received celecoxib at a dose of ≥100 mg per day (dosed as 50 mg BID). Without regard to the duration of exposure, this yields a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/1000 and 1/10,000. Less information, obviously, will be available regarding the incidence rates for adverse events.

With regard to the duration of exposure, very few subjects (39) in the arthritis trials were exposed to celecoxib for >6 months as part of a controlled trial (active or placebo). A larger number (1809) were exposed for >6 months as part of open-label arthritis studies. As a consequence of this, the detection of common AEs that result from chronic exposure (i.e., myocardial infarction, elevated blood pressure), will simply be impossible, since no comparison group is available. More uncommon severe AEs (i.e., vasculitis, pancytopenia) may be detected as occurring in the open-label data, although their incidence will be impossible to determine.

3.3.2 Comment on Data Quality and Completeness

Specifics regarding the completeness of the database for NDA 20-998 will be made during the reviews of the three 'renal' trials, and in the combined Renal/ Cardiac Safety Review (section 4.0 to 4.2 below).

Regarding overall patient exposure, the ability to detect an effect of long-term exposure to celecoxib on AEs is limited by the lack of control data beyond 12 weeks. Inferences regarding long-term toxicity must therefore be drawn from the longer-term open-label data.

Regarding lab data collection, follow-up for abnormal laboratories was dependent on the individual investigators.

Regarding the renal safety review, no information about the acid-base status of any individuals was collected as part of the NDA (i.e., no serum bicarbonates, no arterial pH measurements). This concern was conveyed to the sponsor, and will be discussed further as part of the Safety review.

Regarding cardiac safety review, no information on ECG abnormalities was routinely collected or analyzed.

The Case Report Forms were submitted for all subjects who withdrew from the studies, including both medical and non-medical drop-outs. These were submitted as PDF files on optical discs, and are sufficient for review.

The datasets were submitted both in SAS and hardcopy.

In summary, the data quality and completeness is acceptable for a medical review with emphasis on the renal and cardiac safety. Specific problems regarding the adequacy of the data are noted at appropriate points in the review document.

4.1 Review of Protocol N49-96-02-010 (abbreviated 010 hereafter)

4.1.1 Title of Study

Clinical protocol to evaluate the effects of celecoxib at doses of 200 mg BID and 400 mg BID on renal function and urinary prostaglandins in healthy elderly subjects.

4.1.2 Sites of Investigation and Investigators

Study was conducted by Gerald Schulman at Vanderbilt University Medical Center.

4.1.3 Background

Initial protocol: August 21, 1996

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Two protocol amendments:

1. *October 15, 1996*

The first protocol amendment had the following aims:

1) To change the days of the Urinary Prostaglandins (PGE and 6-keto-PGF) collection.
2) To change the Schedule of Observations and Procedures which is a result of this amendment.
3) To change the Case Report Forms (CRFs) which are a result of this amendment.
4) To correct the Baseline Physical CRF.

2. *January 2, 1997*

This amendment changed the status of this study from a "double-blind" study to a "single-blind" study.

4.1.4 Study Design

This was a single-center, single-blind, randomized, active-controlled, multiple-dose, crossover study to determine the effect of celecoxib on renal function and urinary prostaglandin excretion in healthy elderly subjects. A group of 29 healthy elderly subjects (19 female and 10 male) who were (b)(4) received either celecoxib 200 mg BID for five days followed by celecoxib 400 mg BID for the next five days, or they received naproxen 500 mg BID for 10 days. After taking one of these treatment regimens and undergoing a seven-day washout period, subjects were crossed over to receive the other treatment regimen. Twenty-four subjects completed both treatment regimens.

Two groups were formed: Sequence A; and Sequence B.

Sequence A received drugs in the following order: celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days, followed by Naproxen 500 mg BID for 10 days.

Sequence B received Naproxen 500 mg BID for 10 days, followed by celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days

Prior to and during each Treatment Period, blood and urine samples were collected for calculation of glomerular filtration rate (GFR). Blood samples were also drawn to measure serum electrolytes, serum creatinine, blood urea nitrogen (BUN), and plasma concentrations of celecoxib and naproxen. Twenty-four hour urine samples were collected daily to determine the urinary excretion of PGE2, 6-keto-PGF1-alpha , electrolytes (sodium, potassium, and calcium), and creatinine. The primary aim of the study was to collect data on the renal effects of celecoxib, especially GFR, urinary PGE_2 excretion, and urinary 6-keto-PGF_1-alpha excretion. In addition, the effects of celecoxib were compared with naproxen, another NSAID with a pharmacokinetic profile similar to celecoxib.

4.1.5 Primary and Secondary Endpoints

There were no specified primary or secondary endpoints in this phase I-II study.

Primary study objectives:

1. Evaluate the effect of celecoxib on renal function in healthy elderly subjects; and
2. Assess the effect of celecoxib on urinary excretion of PGE2 and 6-keto-PGF1

Secondary study objectives:

1. Compare the effects of celecoxib 200/400 mg and naproxen 500 mg on renal function and urinary excretion of PGE2 and 6-keto-PGF1-alpha in healthy, elderly subjects; and

2. Evaluate the safety and pharmacokinetics of celecoxib 200/400 mg compared to naproxen 500 mg administered in elderly subjects for 10 days.

4.1.6 Number of subjects/ randomization

A total of 24 evaluable subjects (16 female and 8 male) completed both Treatment Periods of the cross-over study.

4.1.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Be age (b)(4) [redacted] of age, inclusive;
2. Have a physical examination that reveals no clinically significant abnormalities, in the Investigator's opinion, during the Pretreatment Visit;
3. Have normal clinical laboratory test results during the Pretreatment Visit or, if abnormal, are not clinically significant in the Investigator's opinion;
4. Have a creatinine clearance estimated to be > 65 ml/min/1.73 m^2 during the 2 Pretreatment Visit;
5. Have a GFR > 60 ml/min/1.73 m^2as measured by Glofil at Pretreatment 2 Admission Visit;
6. Have blood pressure ≤ 150/90 during the Pretreatment Visit;
7. Have a negative drug toxicology screen during the Pretreatment Visit;
8. Have a negative hepatitis B surface antigen test obtained during the Pretreatment Visit;
9. Weigh ≤ 45 kg and must be within ± 30% of ideal body weight; and
10. Have provided written informed consent prior to admission to this study.

Exclusion Criteria

1. a history of any clinically significant illness, in the Investigator's opinion, within the three months prior to the Pretreatment Visit;
2. a history of hypersensitivity (e.g., anaphylactoid or cutaneous reaction) to cyclooxygenase inhibitors, sulfonamides or iodine;
3. taken any NSAID within 10 days before receiving the first dose of study medication;
4. used any medication within 14 days prior to or before Treatment Period I with the following exceptions: estrogen therapy, bulk laxatives, <325 mg aspirin daily and Maalox for GI symptoms; phenergan or compazine may be taken during the Glofil procedure only;
5. a history of significant substance abuse, drug addiction or alcoholism in the last 3 years;
6. used a tobacco product 48 hours prior to the first dose of study medication;
7. urinary incontinence;
8. presence of anemia (hematocrit < 36.0%; hemoglobin < 12.1 g/dL) during Pretreatment Visit);
9. inability to abstain from sexual activity from 48 hours (Day -4) prior to the time of admission to the study unit until the end of each Treatment Period (males only);
10. received any investigational medication within 30 days prior to Treatment Period I or is scheduled to receive an investigational drug other than study medications described in this protocol, during the course of this study; or,
11. been previously admitted to this study.

4.1.8 Dosage/ Administration

Two groups were formed: Sequence A; and Sequence B.

Sequence A received drugs in the following order: celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days, followed by Naproxen 500 mg BID for 10 days.

Sequence B received Naproxen 500 mg BID for 10 days, followed by celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days

4.1.9 Duration/ Adjustment of Therapy

Reasons for subject discontinuation from the study:

1. The subject develops symptoms that require medical intervention.
2. The subject develops an intercurrent illness that would require non-study medication.
3. If the subject's serum creatinine increases by 50% or if the subject's GFR decreases by 30%, the subject should be discontinued from the study. If the changes in the serum creatinine and GFR are discrepant, the subject will be reevaluated.
4. The subject withdraws his/her consent.
5. The Investigator determines it to be in the subject's best interest.
6. Searle discontinues the study.

4.1.10 Safety and Efficacy Endpoints Measured

Table 4.1.10.1 Timetable for clinical observations and lab measurements in the protocol #010[a].

Procedure/ Test	Pre-Tx -16 t –3	Pre-Tx -2	Baseline -1	Treatment Period 1 Days 1-10	Washout Days 11-17	Period 2 (As 1)	Early Term.
History	X						
Physical	X		X	X	X		X
Hepatitis B Screen	X						
Clinical Labs[i]	X			X[b]		X	X
Serum BUN/ Crt				X[c]		X	X
Creatinine clearance	X						
Vital Signs/ weights	X			X[d]		X	X
ECG	X						
Drug/ Alcohol Screen		X			X		
Urine Na, K, and Vol.		X	X	X[e]	X	X	X
Urine Prostaglandins		X	X	X[f]	X	X	X
GFR				X[g]		X[g]	
Celecoxib Levels				X[h]		X[h]	
Adverse Events			X	X		X	X

a. Data from NDA volume 1.134, table 3.
b. On days 1 and 10.
c. On days 1, 6, and 10.
d. On days 1, 3, 5, 7, 6, and 10.
e. Daily for days 1-10.
f. Days 1, 3, 4, 6, 8, and 9.
g. Days 1 and 6.
h. Days 1, 5, 6, and 10.
i. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, protein, microscopic analysis).

4.1.11 Statistical Considerations

Sample Size

This is a double-blind, randomized, comparator controlled, crossover, 10 day multiple dose study. A total of 24 evaluable subjects (16 female and 8 male) will complete the study. The sample size of 24 evaluable subjects was calculated based on a published standard deviation in change of GFR from control to naproxen of 8.5 mL/minute. Assuming that the within-subject variability of celecoxib and naproxen in this study is the same as in that published study, a sample size of 24 subjects for the study will be sufficient to detect a difference of a GFR reduction of 10% in celecoxib versus a GFR reduction of 25% in naproxen at an alpha level of 0.05 and power of 80%.

Multiplicity

No adjustment for multiplicity was proposed.

Interim Analyses

There were no interim analyses.

Statistical Analysis

1) Statistical Methods for study 010

Treatment difference between celecoxib and naproxen were tested and 95% confidence intervals of the mean difference calculated, based on the log-transformed data and ANOVA for the standard two-way crossover design. First-order of carryover (from the first treatment to the second baseline and second-order carryover (from the first treatment to the second treatment) was investigated, and if normality could not be assumed on either the original or the log-transformed scale, a nonparametric procedure appropriate for this crossover design was used in the analysis.

4.1.11 Statistical Considerations (cont)

Exploratory Analysis

For the celecoxib treatment, an exploratory linear regression analysis will be performed with the observed AUC as an independent variable and change from baseline in urinary prostaglandins on Days 5 and 10 as the dependent variable. A plot was provided between the dependent variable and the independent variable to graphically depict the results and check any non-linearity. In addition, an analysis with AUC replaced by C_{max} was performed. An exploratory linear regression analysis was performed with the 4-hr plasma samples on Days 1 and 6 as the independent variable and change in GFR as the dependent variable.

Safety Analysis

Safety was analyzed by looking at the incidence of treatment-emergent adverse events, changes in laboratory values from baseline, vital signs and temperatures, and physical examinations. AEs were collected during the period of the trial, with no follow-up for AEs after subject discharge.

4.1.12 Efficacy Outcomes for protocol

4.1.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 29 healthy elderly subjects enrolled in study 010 are summarized below. The subjects were broken into two groups, depending on the order in which they received celecoxib and naproxen.

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Table 4.1.12.1.1 Demographics of protocol #010[a].

Demographic	Sequence A	Sequence B
Total Randomized	14	15
Gender		
Male	6 (43%)	4 (27%)
Female	8 (57%)	11 (73%)
Race (n (%))		
Caucasian	14 (100%)	15 (100%)
Black	0 (0%)	0 (0%)
Hispanic	0 (0%)	0 (0%)
Age (yrs) (Mean±sd)	69.6±3.6	70.7±4.5
Mean Weight, kg (±SD)	70±16	72±11
Baseline GFR (ml/min/1.73 m^2)		
Day 2	83±17	82±9
Day 6 of washout	86±18	77±6

a. Data from NDA volume 1.134, Table 5.

4.1.12.2 Disposition of Subjects

Fewer subjects in the high-dose group completed the trial, with 5/7 drop-outs in this group being due to clinical AEs.

Table 4.1.12.2.1 Summary of subjects entered into study 010[a].

	Celecoxib	Naproxen
Entered	14	15
Completed	12	12
Discontinued: Total	2	3
Protocol Non-compliance	2	3
AEs	0	0
Other	0	0

a. Data from NDA volume 1.134, table 3.

4.1.12.2a Subject Selection

No information is available about subject selection in study 010.

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4.1.12.2b Protocol Violations & Deviations

Six subjects had minor protocol violations at time of entry, related to inclusion criteria. These were judged by the sponsor to be not of clinical significance and all subjects were continued in the study.

Five subjects did not complete the study due to receipt of excluded or inappropriate drug (3) or due to difficulty completely GFR measurement (2).

4.1.12.2c Concomitant Therapies used after Trial Initiation

No information about concomitant medications is available.

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4.1.12.2d Analyses of Study 010 Results

Changes in GFR

When data from both period one and two were used, mean GFR at Baseline was 80.0 mL/min/1.73 m^2 prior to celecoxib administration and 84.3 mL/min/1.73 m^2 prior to naproxen treatment. Mean GFR was unchanged with celecoxib averaging 0.86 ml/min/1.73 m^2 below Baseline on Day 1 (200 mg BID) and 1.1 ml/min/1.73 m^2 below Baseline on Day 6 (400 mg BID). In contrast, with naproxen mean GFR was 5.3 mL/min/1.73 m^2 lower than Baseline on Day 1 and 7.5 mL/min/ 1.73 m^2 below Baseline on Day 6, representing a 6% and a 9% decline in GFR, respectively. A statistically significant reduction (p=0.004) in GFR with naproxen was detected on Day 6 when compared to the effect of celecoxib. These results are shown graphically and in tabular form below.

Figure 4.1.12.1 Changes in GFR during Study 010

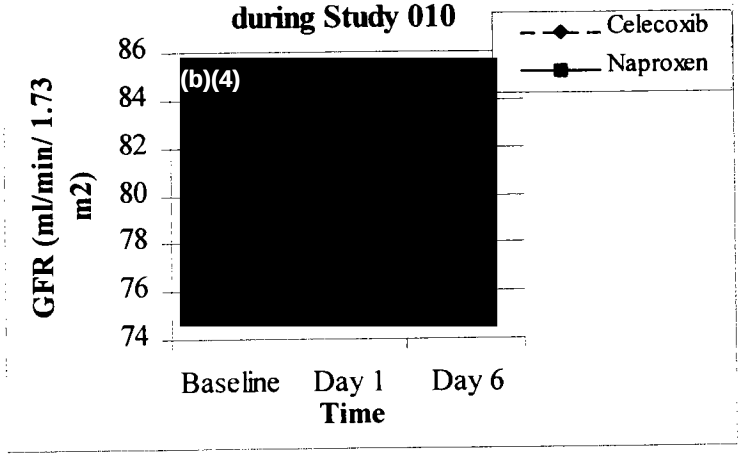


Table 4.1.12.2.2d.1 Changes in GFR during study 010[a].

Period and Group measured Mean±SD (Change from Baseline)	Celecoxib group	Naproxen group
All Evaluable Subjects (n=24)		
GFR at baseline	80±12.8	84±14
GFR on Day One	79.2±13 (-0.864)	79.0±19 (-5.31)
GFR on Day Six	78.9±14 (-1.110)	76.8±19 (-7.53) [b]
Subjects during Period One (n=12)		
GFR at baseline	83.3±16	82.4±12
GFR on Day One	81.5±10 (-1.7)	82.2±12 (-0.148)
GFR on Day Six	81.2±12 (-2.0)	74.7±6 (-7.6)

a. Data from NDA volume 1.134 Table 9.

b. Indicates nominal significance for comparison from baseline p<0.05.

For the patients who initially received naproxen (sequence B), there was not complete return to baseline GFR at the end of the 6 day washout period. Due to this potentially confounding factor, an analysis of the first period alone was also performed. For this group, GFR was largely unchanged in the naproxen group at day one (-0.148 from baseline). A larger decline in GFR was seen at 6 days of naproxen therapy (-7.6). For the subjects who received celecoxib, the mean changes in GFR for days one and six were -1.8 and -2.1 ml/min/1.73 m^2 respectively. There was no significant differences between the effects of naproxen and celecoxib on GFR at either 1 or 6 days when period one was analyzed separately (see table below).

4.1.12.2d Analyses of Study 010 Results (cont)

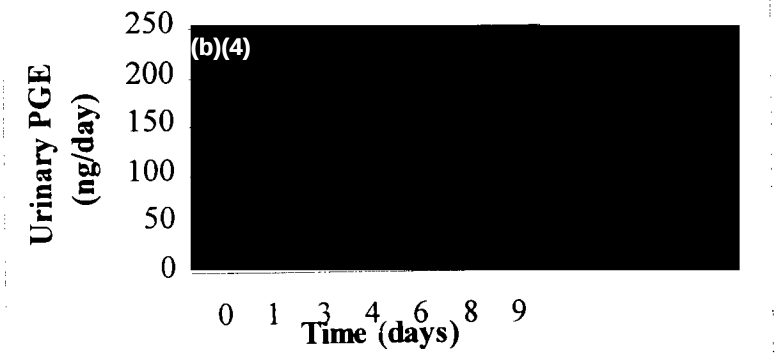
From both periods, there were also 5 individuals in the Naproxen group who had a greater than 20% decrease in GFR measured at either day one or six. No individual in the celecoxib group had a similar decline.

Changes in urinary PGE_2 excretion

Urinary PGE_2 excretion was measured at pretreatment (Days –2 and Washout Day 6), Baseline (Days –1 and Washout Day 7), and Days 1, 3, 4, 6, 8, and 9 of each Treatment Period. For all evaluable data, there was a statistically significant reduction ($p<0.042$) in the urinary excretion of PGE_2 from baseline with celecoxib and naproxen administration. The magnitude of this reduction was consistent across the treatment interval for both celecoxib (-51 to -72%) and naproxen (-71 to -80%) and was not affected by the increase of the celecoxib dose from 200 mg BID to 400 mg BID on Day 6 (although the sample size was small to detect such a difference).

One individual (#9208) excreted 3X more PGE_2 than the standard deviation for the mean of the entire group. While his results are included in the results discussed above, the graph below shows the time-course of prostaglandin inhibition for the two groups minus the data from subject #9208. There was no significant difference between the two groups with regard to the degree of inhibition of PGE_2 release.

Figure 4.1.12.2d.2 Time-course for Urinary Prostaglandin Production in Study 010

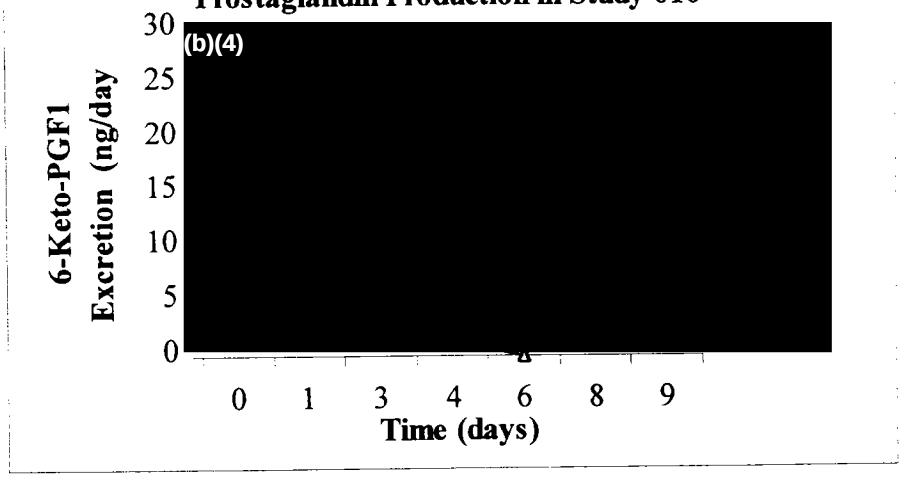


Changes in urinary 6-Keto-PGF_{1}-alpha excretion

Urinary PGF1 excretion was measured at pretreatment (Days –2 and Washout Day 6), Baseline (Days –1 and Washout Day 7), and Days 1, 3, 4, 6, 8, and 9 of each Treatment Period. At Baseline, urinary excretion of 6-keto-PGF1 averaged 28.22 ng/day and 31.46 ng/day in the celecoxib and naproxen treatments, respectively. Urinary 6-keto-PGF1 excretion was significantly reduced ($p<0.013$) by both treatments on Day 1, Day 3, Day 4, Day 6, Day 8 and Day 9. The mean amount of PGF1 excreted decreased ranged (b)(4) for celecoxib and from (b)(4) with naproxen treatment. In a majority of subjects, 6-keto-PGF1 concentrations in urine fell to undetectable levels (<10 pg/ml) at most time points following celecoxib or naproxen administration. This analytical limitation creates uncertainty as to the true magnitude of the reduction in urinary 6-keto-PGF1 excretion with either treatment. Mean decreases in urinary 6-keto-PGF1 excretion were comparable for celecoxib 200 mg BID and 400 mg BID doses. No significant differences were detected between celecoxib and naproxen throughout the treatment interval ($p>0.067$).

If a similar analysis was performed after excluding subject #9208, baseline urinary excretion of 6-keto-PGF1 averaged 21.49 ng/day and 28.42 ng/day for celecoxib and naproxen, respectively. The reduction from baseline in urinary 6-keto-PGF1 excretion with celecoxib 200 mg BID and 400 mg BID ranged (b)(4) (b)(4) In comparison, the mean reduction from Baseline with naproxen ranged from (b)(4) The reductions in urinary 6-keto-PGF1 excretion appeared to be greater with naproxen when compared to celecoxib, and reached statistical significance on Day 3 and Day 6 ($p<0.041$). This data is presented in the figure below.

Figure 6.1.2.12.2d.3 Time-course for Urinary Prostaglandin Production in Study 010



Gender differences in prostaglandin excretion

In a sub-set analysis, the sponsor examined the role of gender in the rates of prostaglandin excretion and the effects of study drugs. Both males and females exhibited sustained decreases in mean urinary 6-keto-PGF1 excretion from baseline with naproxen and celecoxib. Males were observed to have mean baseline urinary 6-keto-PGF1 excretion rates about twice that of females. In both males and females, urinary 6-keto-PGF1 excretion fell dramatically and often to undetectable levels with either treatment.

Excretion of sodium, calcium, potassium, and creatinine

Excretion of these cations and creatinine were measured throughout the trial. The results are presented in tabular form below.

For sodium, celecoxib and naproxen were associated with comparable effects on urinary sodium excretion for both the magnitude of the observed changes and the temporal pattern. Pairwise comparisons using repeated measures ANOVA revealed no clinically significant differences between treatments. There was also no significant difference in urinary sodium excretion between the 200 and 400 mg doses of celecoxib (see table below).

Overall, both drugs were associated with sodium retention. On a cumulative basis, subjects retained an average of at least 160.4 mmol of sodium on Days 1 through 9 of celecoxib treatment compared to 29.9 mmol of sodium retained during 9 days of naproxen treatment (a nominally significant difference). This occurred at a time when dietary intake of sodium was relatively constant throughout the study and similar to the baseline period.

For potassium excretion, there were no statistically significant differences observed between treatment groups with regard to change from baseline at any time point (see table below) for urinary potassium excretion.

For calcium excretion, urinary calcium excretion was not affected by celecoxib or naproxen administration, when compared to urinary calcium excretion at baseline. There were no statistically significant differences between treatment groups with regard to change from baseline at any time point.

With regard to urinary creatinine excretion, it was not affected by celecoxib or naproxen treatment, when compared to baseline urinary creatinine excretion. There were no statistically significant differences between treatment groups with regard to change from baseline at any time point.

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4.1.12.2d Analyses of Study 010 Results cont)

Table 4.1.12.2d.2 Changes in urinary excretion of sodium, potassium, calcium and creatinine during study 010[a].

Period and Group measured Mean±SD (Change from Baseline)	Celecoxib group	Naproxen group
Urinary Sodium (mmol/day)		
Baseline	137.4±50	126.9±33
Day 1	96.7±24	78.4±26
Day 5	131.6±40	147±55
Day 9	124.8±49	141±58
Urinary Potassium (mmol/day)		
Baseline	53.6±18	54.2±18
Day 1	48.6±17	49.1±20
Day 5	57.0±19	78.9±85
Day 9	59.0±26	63.0±22
Urinary Calcium (mmol/day)		
Baseline	6.9±3.4	7.2±3.4
Day 1	6.4±3.5	6.3±2.9
Day 5	7.2±3.9	8.0±3.5
Day 9	6.9±3.6	8.1±4.6
Urinary Creatinine (mmol/day)		
Baseline	8.5±2.6	9.0±2.6
Day 1	8.2±2.2	8.4±2.4
Day 5	8.5±2.2	8.7±2.4
Day 9	8.2±2.4	8.7±2.8

a. Data from NDA volume 1.134 Tables 12-15. Shown are representative days. See NDA for full data.

4.1.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 4.1.13.1 Clinical adverse experience (AE) summary from protocol #010[a].

Clinical event shown as # of subjects (% of 26 exposed subjects)	Celecoxib 200 mg BID	Celecoxib 400 mg BID	Naproxen 500 mg BID
With Any AE	7 (27%)	12 (46%)	15 (56%)
With Serious AE	0 (0%)	1 (4%)	0 (0%)
Discontinued due to an AE	0 (0%)	0 (0%)	0 (0%)
Discontinued due to Lab AE	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.134.

4.1.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.1.13.2 Comments on Specific Safety Parameters

Deaths

No deaths occurred during the trial.

Serious Adverse Events

One serious adverse event occurred in the celecoxib 400 mg dose group.

Subject No. US0001-0204, (Injury-Accidental), was a 68-year-old male with a history of cerebellar ataxia, appendectomy, pilonidal cyst and urolithiasis. The subject was enrolled into the study on 17 January 1997 and randomized into Treatment Sequence 1. Three days after completion of the first study period (i.e., treatment with celecoxib 200/400 mg BID), the subject was struck while driving his car. He was hospitalized for an overnight observation and administered i.v. Toradol for pain along with deep heat treatments. The subject was released the following day in stable condition. No lacerations or fractures were noted. The subject was removed from the study due to the criteria set forth in the protocol (Protocol Non-compliance).

4.1.14 Study 010 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were healthy elderly individuals.

1. After six days, there was a small, significant, decrease in GFR in the patients who received naproxen (averaging 7 cc/min of creatinine clearance, see table 4.1.12.2.2d.1). Patient who took celecoxib for the same period of time had a smaller decline in GFR (1-2 cc/min of creatinine clearance). This result was driven by 5 individuals with a >20% decline in their GFR (see below).

2. After 6 days, more individuals in the naproxen group had declines in GFR of >20% (5) compared with the celecoxib group (0).

3. Both celecoxib and naproxen inhibit PGE_2 and 6-keto-PGF_1 excretion (see figures 4.1.2.12.2d.2 and 3). While both drugs inhibited PGE_2 excretion equally, there was a trend towards greater inhibition of 6-keto-PGF_1 excretion by naproxen.

4. Administration of both celecoxib and naproxen were associated with sodium retention (see table 4.1.12.2.2d.2). There were no significant effect of either celecoxib or naproxen on calcium, potassium, or creatinine excretion.

4.1.15 Study 010 Safety Summary

1. There were no deaths and one Serious Adverse Event, unrelated to celecoxib administration.
2. There were no incidences of acute renal failure.

4.1.16 Study 010 Reviewer's Conclusions

With regard to efficacy, this trial in healthy elderly demonstrates that both naproxen and celecoxib inhibit the excretion of both PGE2 and 6-keto-PGF1. The use of celecoxib for 6 days in this study was associated with a slightly smaller decline in GFR. This was driven by wide subject variability in the naproxen group (5 subjects had a >20% decline in GFR). Both naproxen and celecoxib cause sodium retention.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

4.2 Review of Protocol E49-96-02-033 (hereafter abbreviated 'study 033').

4.2.1 Title of Study

Clinical protocol to evaluate the effects of SC-58635 (celecoxib) and Naproxen on renal function and urinary prostaglandins in sodium and volume depleted subjects.

4.2.2 Sites of Investigation and Investigators

Study was conducted by Hans Brunner, M.D., at the University Hospital, Lausanne Switzerland.

4.2.3 Background

Initial protocol: August 21, 1996

Protocol amendments:

There were three protocol amendments, dated October 23 and 28, 1996, and 12 November 1996. All three amendments dealt with minor administrative changes.

4.2.4 Study Design

This was a single-center, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group, outpatient study. Forty-two (42) subjects were randomized to receive either celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo BID for six consecutive days followed by a single morning dose on the seventh day. A listing of the safety and efficacy measurements is found in the table below.

PreTreatment Phase (Day –14 to –5)

Following screening, the subject had samples collected for several baseline values: prostaglandin excretion; hormone levels; and renal function. The subjects' renal function was evaluated at the second Pretreatment Visit. GFR was calculated from a sinistrine clearance procedure and RBF was calculated using PAH clearance. The fractional excretion of sodium, lithium, and potassium were also calculated from the appropriate urine and serum samples.

Low Sodium and Low Volume Period (Day -4 through Day -1)

The low sodium and low volume period consisted of the four days immediately prior to the start of study drug administration. Subjects were outpatients during this period, but took all low sodium meals (3 g/day or approximately 50 mmol/day) at the investigative site. On Day -4, each subject received a single dose of furosemide 40 mg.

Treatment Period (Day 1 through Day 7)

The treatment period was the seven days during which subjects received study medication in randomized, blinded fashion. Subjects were outpatients, but continued to report to the investigative unit for all meals. Study medication was administered every 12 hours during the first 6 days, and on the morning of day 7. Subjects whose urinary sodium excretion was ≥75 mmol/day for two consecutive days during this period were to be withdrawn from the study, as it was assumed that they had been noncompliant with the study diet. They were to be replaced. Renal Blood Flow (RBF) and GFR were measured at the end of hospital day 6, as it was in the pre-treatment period.

Posttreatment Period (Day 8)

Subjects returned to the investigative unit on Day 8 for a final physical examination, measurement of vital signs and weight, and clinical laboratory tests including hematology, clinical chemistry, and urinalysis (including a final 24 hour urine collection for prostaglandin excretion).

4.2.5 Primary and Secondary Endpoints

Primary study objectives:

The primary objectives of this study were to:

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups; and

2. Compare the changes in urinary PGs (PGE_2 and 6-keto-PGF1-alpha , a metabolite of prostacyclin, PGI_2) from predose (Day -2 and Day -1) through Day 7 postdose, between the celecoxib and naproxen treatment groups.

4.2.5 Primary and Secondary Endpoints (cont)

Secondary study objectives:

The secondary objectives of this study were to evaluate the changes between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7 for:

1. Renal blood flow (mL/min);
2. Plasma renin activity (ng angiotensin I released /mL/hr);
3. Plasma aldosterone (pg/mL) and plasma atrial natriuretic peptide (fmol/mL);
4. Fractional urinary sodium, potassium, and lithium clearances; and
5. Serum thromboxane (ng/mL).
6. The safety and pharmacokinetics of celecoxib in sodium- and volume-depleted healthy subjects. A safety measure of particular interest (per the sponsor) was the 24-hour uric acid concentration on Days 1, 3, and 7. Pharmacokinetic variables of interest were the plasma concentrations of celecoxib and naproxen on Days 1 and 7, and the urinary concentrations of celecoxib metabolite celecoxib on Days 1 and 7.

4.2.6 Number of subjects/ randomization

A total of 24 evaluable subjects (16 female and 8 male) completed both Treatment Periods of the cross-over study.

4.2.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Been a male between (b)(4) of age inclusive;
2. Had a physical examination during the Pretreatment Period that revealed no clinically significant abnormalities;
3. Had normal clinical laboratory test results during the Pretreatment Period or, if abnormal, were not clinically significant;
4. Had a GFR > 100 mL/min/1.73 m^2 during the Pretreatment Period;
5. Had normal blood pressure (BP < 140/90 mmHg) during the Pretreatment Period;
6. Had a negative drug screen during the Pretreatment Period;
7. Had a negative HIV screen during the Pretreatment Period;
8. Had a negative hepatitis B surface antigen screen during the Pretreatment Period;
9. Weighed >50 kg and been within 20% of ideal body; and
10. Provided documented written informed consent prior to admission to this study.

Exclusion Criteria

1. A history of any clinically significant illness within the three months prior to the start of the Pretreatment Period;
2. A history of hypersensitivity (e.g., anaphylactoid or cutaneous reaction) to COX inhibitors or sulfonamides, or a history of lactose intolerance;
3. Used any NSAIDs within 10 days of the start of the Pretreatment Period or other medications within 14 days of the start of the Treatment Period;
4. A history of substance abuse, drug addiction, or alcoholism within the last three years;
5. Used a tobacco product or consumed alcohol within 48 hours prior to the Pretreatment Period or were unable to abstain from tobacco and alcohol products throughout the entire length of the study;
6. Urinary incontinence;
7. Anemia (hemoglobin <13 g/dL and hematocrit <39%);
8. Received any investigational medication within 30 days prior to this study, or were expected to receive any investigational medication during the study;
9. An inability to abstain from any sexual activity from Day -4 throughout the entire length of the study; or,
10. Been previously admitted to this study.

4.2.8 Dosage/ Administration

Forty-two (42) subjects were randomized to receive either celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo BID for six consecutive days followed by a single morning dose on the seventh day.

4.2.9 Duration/ Adjustment of Therapy

Reasons for subject discontinuation from the study:

1. Urinary sodium values were ≥75 mmol/L for two consecutive days during the Treatment Period or on both Day -2 and Day -1 of the Low Sodium and Low Volume Period;
2. Serum creatinine increased by 50% over Pretreatment assessments;
3. The subject was sexually active during the study;
4. Developed symptoms that required medical intervention;
5. Developed an intercurrent illness that required any concomitant medication;
6. Withdrawal of consent;
7. The Investigator determined it was in the subject s best interest to withdraw; or
8. Searle discontinued the study.

4.2.10 Safety and Efficacy Endpoints Measured

Table 4.2.10.1 Timetable for clinical observations and lab measurements in study 033[a].

Procedure/ Test	Pre-Tx	Low-Na^+, Low-Volume Period				Treatment Period							Post-Tx Period
	-14 to -5	-4	-3	-2	-1	1	2	3	4	5	6	7	8
History	X												
Physical	X					X							
Drugs, Hepatitis B/ HIV Screen	X												
Clinical Labs[b]	X					X		X					X
Urine Vol, Na, K, Crt	X		X	X	X	X[c]	X	X[c]	X	X	X	X[c]	
Na, Li, K clearance	X		X	X	X	X	X	X	X	X	X	X	
Vital Signs/ weights	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X												
Serum Thromboxane						X						X	
Urine Prostaglandins	X		X	X	X	X	X	X	X	X	X	X	
GFR, RBF	X					X						X	
Low-Na^+ Diet		X	X	X	X	X	X	X	X	X	X		
Lasix, 40 mg		X											
Celecoxib Levels						X						X	
Adverse Events						X							

a. Data from NDA volume 1.137, table 1.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, RBC/hpf, protein, glucose, ketones, bilirubin).

c. Urinary uric acid was also measured.

4.2.11 Statistical Considerations

Demographics and Baseline Characteristics

All randomized subjects were included in these analyses. Baseline demographic characteristics (age and race) were summarized within treatment groups and descriptive statistics (i.e., mean, standard deviation, median, and range) were calculated. The groups were compared with respect to demographics, including baseline renal function values, using the Kruskal-Wallis test, and with respect to race using the Fisher's Exact test.

Subject Population Analyzed

All analyses relating to renal function were performed on the Intent-to-Treat (ITT) Cohort (all randomized subjects who took at least one dose of study medication).

4.2.11 Statistical Considerations (cont)

Glomerular Filtration Rates

Changes from predosing to postdosing GFRs were summarized and descriptive statistics were provided. Overall differences among treatments using a Kruskal-Wallis test and paired t-tests. Pairwise comparisons were also carried out for the differences between celecoxib 200 mg and naproxen groups, celecoxib 200 mg and placebo groups, celecoxib 400 mg and naproxen groups, celecoxib 400 mg and placebo groups, and celecoxib 200 mg and celecoxib 400 mg groups using a repeated-measures ANOVA model.

Renal Blood Flow (RBF) and Fractional Excretion of Sodium, Potassium, and Lithium

Except for plotting mean RBF values, or mean fractional excretion of sodium, potassium, and lithium against study drug plasma concentrations, the statistical analyses for these secondary variables of interest were identical to that for GFR, described above.

Renal Prostaglandins

Pairwise comparisons between the effects of treatments on urinary prostaglandins were carried out for the differences between the celecoxib 200 mg and naproxen groups, celecoxib 200 mg and placebo groups, celecoxib 400 mg and naproxen groups, celecoxib 400 mg and placebo groups, and celecoxib 200 mg and celecoxib 400 mg groups. The differences also were analyzed using a repeated-measures ANOVA model.

Serum Thromboxane, Plasma Renin Activity, Plasma Aldosterone, and Atrial Natriuretic Peptide

Serum TxB2, plasma PRA, aldosterone and ANP values on Days 1 and 7 were summarized and descriptive statistics were provided. Mean changes for each variable from their respective daily predosing values were summarized and overall differences were analyzed using an ANCOVA with Baseline as the covariate. PRA, and plasma aldosterone and ANP values were not analyzed statistically, but are presented by subject in the data listings.

Pharmacokinetic Data

Plasma concentrations of study medication are listed by subject in the data listings. Summary statistics for the plasma concentrations of celecoxib and naproxen are provided by dose group and by study day. Summary statistics for the urinary concentrations of the celecoxib metabolite SC-62807 are presented by dose group and study day.

Statistical Determination of Sample Size

The sample size of 10 subjects per treatment group was based on clinical judgment. Assuming a standard error of 3 mL/min/1.73 m^2 at both Day 1 and Day 4 and coefficient of correlation between the Day 1 and Day 4 measurements of 0.5, the intra-subject standard deviation can be estimated as 7.35 mL/ min/1.73 m^2 . A mean difference in change from Baseline in creatinine clearance between two treatment groups of 9.74 mL/min/1.73 m^2 or larger can be detected with a sample size of 10 subjects per treatment group, assuming an intra-subject standard deviation of 7.35 mL/ min/1.73 m^2, at a significance level of 0.05 (two-sided) and 80% power. Using a standard deviation for the change in urinary urinary-6-keto-PGF1 of 2.1 ng/hour, a difference in mean change from Baseline in urinary-6-keto-PGF1 D between two treatment groups of 2.78 ng/hour or larger can be detected with a sample size of 10 subjects per treatment group, assuming a standard deviation of 2.1 ng/hour, at significance = 0.05 and 80% power.

Statistical/Analytical Issues

The sponsor used Day -1 data to compute Baseline urinary PGs instead of an average of the Day -2 and Day -1 values since the Day -1 data were collected closer to the initiation of dosing on Day 1. All calculations involving 24-hour urine collections were done using the actual duration of urine collection. An ad hoc analysis was performed to calculate the intra-subject variance of the two predose GFR, RBF and partial sodium, potassium and lithium clearance values that were obtained on Days 1 and 7. This analysis was performed because there appeared to be considerable variation in these values.

Handling of Missing Data

There were no imputation methods used for missing data in the analysis.

Multiplicity

No adjustment for multiplicity was proposed.

4.2.11 Statistical Considerations (cont)

Interim Analyses

There were no interim analyses.

Safety Analysis

Every randomized subject who received study medication was included in the safety analysis. All adverse events were coded and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated and tested for significance using a paired t-test. Clinical laboratory data also were summarized and treatment groups compared using the Kruskal-Wallis Test applied to change from Baseline. Using a Chi-square test, shifts in laboratory values were compared across treatment groups in terms of the number of subjects showing an increase, decrease, and no change, with respect to the normal range. Values outside the normal range at Baseline and Posttreatment were identified and presented in a 3x3 shift table by treatment group. Depending on the number of non-zero cells, the Stuart-Maxwell Test or the McNemar's Test was used to determine significant distributional changes from Baseline to Posttreatment within treatment group. Scatter plots were used to graphically depict the results. The incidence of clinically relevant changes in laboratory tests from Baseline to Posttreatment was tabulated by treatment group.

Laboratory values considered to be clinically relevant are listed in the table that follows:

SGOT (AST): ≥3 x upper limits of normal (ULN)
SGPT (ALT): ≥3 x ULN
Alkaline Phosphatase: ≥1.25 x ULN
Total Bilirubin: ≥1.5 x ULN
Creatinine: ≥1.3 x ULN
BUN: ≥2.0 x ULN
Hematocrit: a decrease ≥5 percentage points (from Baseline value)
Hemoglobin: a decrease ≥2 g/dL (from Baseline value)
WBC: <3000/PL
Platelets: <100,000/PL

Summary statistics for vital signs and body weight and mean changes from Baseline to Posttreatment were calculated and compared across treatment groups using the Kruskal-Wallis Test.

4.2.12 Efficacy Outcomes for protocol

4.2.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 42 subjects enrolled in protocol #033 are summarized below. Note that there was a significant difference in between the two 'baseline' GFRs measured prior to study drug administration in the celecoxib 200 BID group.

Table 6.2.3.12.1.1 Demographics of protocol #033[a].

Demographic	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
Gender				
Male	11 (100%)	11 (100%)	10 (100%)	10 (100%)
Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race (n (%))				
Caucasian	10 (91%)	10 (91%)	9 (90%)	9 (90%)
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic	1 (9%)	1 (9%)	1 (10%)	1 (10%)
Other				
Age (yrs) (Mean±sd)	23.3±3	26.4±5	23.0±3	24.5±5
Mean Weight, kg (±SD)	74±5	74±6	74±11	78±8
Baseline GFR (ml/min/1.73 m^2)				
Pretreatment	119±13	134±13	121±23	127±10
Day 1, Pre-dose	117±12	101±19[b]	104±18	115±21

a. Data from NDA volume 1.137, Table 4.

b. P value <0.001 comparing two GFRs for celecoxib 200 mg BID group.

4.2.12.2 Disposition of Subjects

The table below shows the disposition of subjects in study 033.

Table 4.2.12.2.1 Summary of subjects entered into protocol #033[a].

	Placebo	Celecoxib 200 BID	Celecoxib 400 BID	Naproxen 500 BID
Entered	11	11	10	10
Completed	10 (91%)	11 (100%)	10 (100%)	10 (100%)
Discontinued: Total	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Protocol Non-compliance	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.137, table 3.

b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.

4.2.12.2a Subject Selection

No information is available about subject selection in protocol #033.

4.2.12.2b Protocol Violations & Deviations

1. Pertaining to dosing with study medication, one subject missed one dose of study medication. Subject 0001 did not receive the second dose of naproxen on Day 3.

2. Related to concomitant medications (which were prohibited in the study), seven subjects took nine concomitant meds. One of these was withdrawn. Concomitant meds used included: hexetidine/ chlorhexidine; azithromycin; acyclovir; topical hydrocortisone; and anti-acne preparation; and acetominophen for a headache.

4.2.12.2c Concomitant Therapies used after Trial Initiation

No concomitant medications were to be used during the trial, and such use constituted a protocol violation.

4.2.12.2d Analyses of Study 033 Trial Results

Primary study objectives

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups.

The effect of short-term administration of celecoxib on GFR was first analyzed by comparing the average GFRs taken before the first dose Days 1 and 7. There were no significant differences between the study groups detected, and no significant decline in mean GFT detected in any dose group. When examined hour by hour (data not shown), no consistent effect of any drug or dose –group on GFR was detected. There was also no evidence of a temporal association between plasma levels of celecoxib and naproxen and changes in GFR. As the sponsor notes…'Changes in GFR were erratic across treatments and the standard errors of treatment means were large, therefore limiting interpretation of the data.' (NDA vol. 1.137, p. 49).

Table 4.2.12.2d.1 Effect of celecoxib and naproxen on GFR in study #033[a].

	Placebo N=11	**Celecoxib 200 BID N=11**	**Celecoxib 400 BID N=10**	**Naproxen 500 BID N=10**
Day One Pre-dose				
Mean±SD	116.8±12	100.7±15	104±115	109±15
Within-subject SD	12.2	15.4	7.0	20.4
Day Seven Pre-Dose				
Mean±SD	116.8±13	105.5±19	101.3±16	125.1±22
Within-subject SD	13.2	18.6	16.5	22.3

a. Data from NDA volume 1.137, table 3.
b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.

2. Compare the changes in urinary PGs (PGE_2 and 6-keto-PGF1-alpha , a metabolite of prostacyclin, PGI_2) from predose (Day -2 and Day -1) through Day 7 postdose, between the celecoxib and naproxen treatment groups.

4.2.12.2d Analyses of Study 033 Trial Results
Primary study objectives (cont)

Urinary PGE_2

For urinary $PGE_2$2, there were no statistically significant differences between study drug groups between the Pre-dose values for Days 1 and 7. There was a large variability in urinary PGE_2 excretion for all treatment groups; the range between observed individuals for many time points was 100-fold or greater. Similarly, pairwise comparison using a repeated-measures ANOVA found no statistically significant differences between treatment groups.

Urinary 6-keto-PGF_1-alpha

Analysis of the 6-keto-PGF_1-alpha excretion was again hindered by extremely wide subject to subject variability. This can be seen below in the wide standard deviations and ranges for the baseline 6-keto-PGF_1-alpha excretion. Note also the higher basal rate of 6-keto-PGF_1-alpha in the naproxen group. The table below shows the changes from baseline for the study groups. Given the broad standard deviations and ranges of individual excretion rates, there was a trend towards decreased 6-keto-PGF_1-alpha excretion in the naproxen group, compared with placebo and the two celecoxib groups. This was particularly true during days 2-6. The celecoxib 400 mg dose group also tended to have lower 6-keto-PGF_1-alpha excretion rates than placebo throughout the study.

Table 4.2.12.2d.2 Effect of celecoxib and naproxen on renal 6-keto-PGF1-alpha excretion in 033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value[b]
Baseline (Day –1)					
Mean±SD	90.4±43	77.7±37	95.0±50	134.0±107	--
Range	(b)(4)				
Difference from Baseline					
Day 1 Pre-dose					
Mean±SD	-16.4±58	-14.2±16	-51.7±36	-72.5±83	0.112
Range	(b)(4)				
Day 2 Pre-dose					
Mean±SD	-3.6±44	-30.0±39	-37.9±35	-89.8±63	0.003
Range	(b)(4)				
Day 3 Pre-dose					
Mean±SD	-15.5±62	-20.0±45	-55.1±17	-88.8±76	0.037
Range	(b)(4)				
Day 4 Pre-dose					
Mean±SD	-3.5±34	-41±35	-61±35	-81±69	<0.001
Range	(b)(4)				
Day 5 Pre-dose					
Mean±SD	-33.8±64	-29.0±27	-61.4±23	-109.4±92	0.036
Range	(b)(4)				
Day 6 Pre-dose					
Mean±SD	-20.6±53	-30.9±33	-65.8±37	-90.9±62	0.014
Range	(b)(4)				
Day 7 Pre-Dose					
Mean±SD	17.3±44	-10.9±33	-40.9±39	-78.1±71	0.002
Within-subject SD	(b)(4)				

a. Data from NDA volume 1.137, table 12.
b. P value using ANCOVA.

Per the sponsor, repeated measures analysis showed significant differences between placebo and both celecoxib 400 mg and naproxen with regard to 6-keto-PGF_1-alpha excretion.

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives:

1. Changes in Renal Blood Flow (RBF) between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The primary times of comparison were between the RBF obtained just prior to the first dose on Day one, and the only dose on Day seven. For this analysis, as shown below, there were no statistically significant differences between treatment groups for any RBF value. The within-subject variability was, as with GFR, approximately 10% (range 5.7 to 19.4%).

Table 4.2.12.2d.3 Effect of celecoxib and naproxen on RBF in study 033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
Day One Pre-dose				
Mean±SD	532.1±96	492.2±79	538.3±118	512.3±88
Median	522.5	476	552	514.3
Day Seven Pre-Dose				
Mean±SD	545.9±73	524.7±96	541.4±130	565.1±53
Median	536.5	505.5	516.5	560.8
P-Value[c]	0.659	0.212	0.886	0.142

a. Data from NDA volume 1.137, table 3.
b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.
c. Using paired t-test comparing day one and day seven, per the sponsor.

2. Changes in serum thromboxane levels between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The mean serum Thromboxane (TxB2) levels for each treatment group are shown below. At day 7, there was a statistically significant effect of naproxen to decrease TxB2 levels, compared with placebo, evident within 2 hours of the first dose. No significant effect of celecoxib on TxB2 levels was detected.

Table 4.2.12.2d.4 Effect of celecoxib and naproxen on serum thromboxane levels in study 033[a].

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	216.5±83	228.2±97	188.7±63	223.8±78	
Range	(b)(4)				
Difference from Pre- to Post-Dose					
Mean±SD	-3.1±64	-21.9±134	-9.3±64	-219.2±77	<0.0001
Range	(b)(4)				
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	185.1±93	219.9±55	222.3±83	16.5±8	
Range	(b)(4)				
Difference from Pre- to Post-Dose					
Mean±SD	24±93	-19.5±50	-30.0±44.8	-13.9±8	0.001
Range	(b)(4)				

a. Data from NDA volume 1.137, table 14.
c. Using ANCOVA, per the sponsor.